

Late Effects in Survivors of Childhood Cancer

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Objectives After completing this article, readers should be able to:

1. Describe common late effects in children who are treated for cancer.
2. Know the common clinical presentations for the more serious late effects.
3. Explain how to monitor survivors of childhood cancer for late effects.
4. Recognize when to refer patients to a pediatric oncologist or other specialist.

Case Presentation

A 19-year-old male was treated for cerebellar medulloblastoma at 3 years of age. Therapy included total resection followed by craniospinal radiation in a dose of 3,600 cGy, with a boost to 5,040 cGy to the tumor bed, as well as chemotherapy with vincristine, cyclophosphamide, and cisplatin. School was a struggle, and he was held back in the 8th grade. One physician suggested methylphenidate therapy, but the boy's mother refused. He has just graduated from high school but is having difficulty obtaining employment. Now he presents with his fiancée because they want to know if he can father children. He shows no evidence of recurrent disease or complications of his tumor.

Physical examination documents a weight of 60 kg (16th percentile) and height of 158 cm (<3rd percentile). Abnormalities include a 3×4 cm area of alopecia over his occipital region and a posterior midline craniotomy scar. His only neurologic deficit is a mild impairment in upward gaze bilaterally. He has no lymphadenopathy or thyroid abnormalities. He is at Sexual Maturity Rating (SMR) 5.

Results of complete blood count, chemistry profile, and thyroid function tests are normal; the insulin-like growth factor value is low. Semen analysis is normal. Audiogram demonstrates mild-to-moderate bilateral sensorineural hearing loss.

The combined radiation and chemotherapy administered to the boy at a relatively young age would be expected to cause neurocognitive dysfunction. School problems are common for children treated with craniospinal irradiation (even older children), who should be evaluated and problems addressed promptly to optimize learning.

Cranial radiation doses of more than 3,000 cGy carry a high risk for endocrinopathies (Table 1). When this young man's growth velocity began to decline, his height deficit could have been minimized by treating him with growth hormone. He also is at risk for central hypothyroidism and secondary adrenal insufficiency due to impairment of the hypothalamic-pituitary axis. Because the risk of endocrine dysfunction increases over time, he should have annual thyroid studies and measurement of early morning cortisol performed. An SMR 5 for pubertal development suggests that his testosterone, luteinizing hormone, and follicle-stimulating hormone concentrations likely are normal. Despite his young age at treatment, he remains at risk for oligo- or azoospermia because he received cyclophosphamide (Table 2).

Permanent alopecia can result from high doses of radiation. This effect typically is seen in areas where the dose of radiation has been increased and focused on the tumor bed.

Both cisplatin and cranial radiation, especially cerebellar, can impair hearing (Tables 1 and 2). Cisplatin-related hearing loss starts in the high-frequency range, but can progress to more global deficits. Earlier detection of the hearing loss and correction with hearing aids may have improved this boy's school difficulties.

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Table 1. Late Effects of Radiation Therapy

Site of Radiation	System	Potential Effects	Monitoring
Brain	Central and peripheral nervous	Cognitive dysfunction, leukoencephalopathy, second CNS tumors	Neurocognitive and psychological testing, MRI when appropriate
		Stroke, ototoxicity, myelitis, blindness, peripheral neuropathy	Neurologic, auditory, and ophthalmic evaluations
	Endocrine	Precocious puberty, growth hormone deficiency, other pituitary and hypothalamic dysfunction	Height and weight, Sexual Maturity Rating staging, history and physical examination, bone age in those growing poorly, free T4, TSH, LH, FSH, testosterone, estradiol
Head and neck	Vision	Obesity	BMI
		Cataracts; corneal, lacrimal duct, retinal, conjunctiva, scleral disease; optic neuropathy	Ophthalmic examination
	Auditory	Tympanosclerosis, otosclerosis, eustachian tube dysfunction, conductive or sensorineural hearing loss	History, audiogram
	Skeletal	Craniofacial abnormalities	Physical examination, psychosocial assessment of adjustment
		Dental abnormalities, salivary changes	Dental examinations and cleaning every 6 months
	Respiratory Endocrine	Chronic sinusitis Hypothyroidism, thyroid nodules or cancer, hyperthyroidism	History and physical examination Thyroid function tests, endocrine consultation when appropriate
Chest/thorax/upper abdomen	Respiratory	Pulmonary fibrosis, delayed interstitial pneumonitis, restrictive/obstructive lung disease	Physical examination, chest radiography, pulmonary function tests
	Cardiac	Cardiomyopathy, pericarditis, coronary artery disease, valvular disease	Blood pressure, electrocardiography, echocardiography, lipid profile, cardiology consultation if needed
	Reticuloendothelial	Functional asplenia with doses of >3,000 cGy	Peripheral blood smear for Howell-Jolly bodies, liver-spleen scan, appropriate evaluation and treatment of fever if hyposplenic
	Hepatic	Hepatic fibrosis, cirrhosis, hepatocellular carcinoma	Physical examination, ALT, AST, bilirubin, AFP in patients who have chronic hepatitis Liver ultrasonography in patients who have cirrhosis
	Secondary malignancy	Breast cancer	Breast self-examination, physical examination, mammography
Lower abdomen/pelvis	Renal	Hypertension, decreased creatinine clearance	Blood pressure, blood urea nitrogen, creatinine, urinalysis
	Gastrointestinal	Bowel obstruction, fistulas, strictures, malignancies	History, physical examination, cancer screening when appropriate
	Endocrine	Ovarian and testicular dysfunction	History, physical examination, LH, FSH, estradiol, testosterone
	Genitourinary	Hemorrhagic cystitis, bladder fibrosis, malignancy	Urinalysis, voiding history
Musculoskeletal	Spine	Scoliosis, kyphosis	Physical examination, spine radiographs
	Extremities	Growth problems: hypoplasia and atrophy, fibrosis, reduced or uneven growth, limb length discrepancy	Physical examination
	Secondary malignancy	Cosmetic deformities Sarcomas	Physical examination

CNS=central nervous system, MRI=magnetic resonance imaging, T4=thyroxine, TSH=thyroid-stimulating hormone, LH=leuteinizing hormone, FSH=follicle-stimulating hormone, BMI=body mass index, ALT=alanine aminotransferase, AST=aspartate aminotransferase, AFP=alpha-fetoprotein

Table 2. Late Effects of Chemotherapy

System	Agent	Potential Effects	Monitoring
Central and peripheral nervous	Intrathecal chemotherapy High doses of methotrexate or cytosine arabinoside	Cognitive dysfunction Leukoencephalopathy, seizures, hemiplegia, neuropsychiatric changes	Neurocognitive evaluation Neurologic evaluation
	Cisplatin	Peripheral neuropathy, hearing loss	Physical examination, audiogram
	Corticosteroids	Cataracts	Eye examinations
Respiratory	Bleomycin, BCNU, and CCNU	Pulmonary fibrosis	Pulmonary function tests with DL _{CO} , chest radiography
Cardiac	Anthracyclines*	Cardiomyopathy, congestive heart failure, arrhythmias	Echocardiography, electrocardiography
Renal	Heavy metals,** ifosfamide	Glomerular or tubular injury, insufficiency	BUN, creatinine, blood pressure, urinalysis
Genitourinary	Cyclophosphamide, ifosfamide	Bladder fibrosis,*** dysfunctional voiding, bladder malignancy	History, urinalysis
Reproductive	Alkylating agents,**** heavy metals	Hypogonadism, infertility, early menopause	History of pubertal development, menstrual cycles, and sexual function; LH, FSH, estradiol, testosterone
Skeletal	Methotrexate, corticosteroids	Osteopenia, osteoporosis Avascular necrosis	Bone density evaluation History, physical examination, radiographs if indicated
Psychosocial	Any cancer experience	Depression, anxiety, posttraumatic stress, social withdrawal, isolation, limitations in health care and insurance	Clinical interview
Hematologic	Alkylating agents, heavy metals, etoposide	Secondary AML	Complete blood count

BCNU=carmustine, CCNU=lomustine, DL_{CO}=diffusing capacity for carbon monoxide, BUN=blood urea nitrogen, LH=luteinizing hormone, FSH=follicle-stimulating hormone, AML=acute myeloid leukemia
 *Daunomycin, doxorubicin, idarubicin
 **Cisplatin, carboplatin
 ***In patients treated for hemorrhagic cystitis
 ****Cyclophosphamide, ifosfamide

Introduction

The overall 5-year survival rate for victims of childhood cancer is now approximately 75%. A long-term survivor can be defined arbitrarily as one having no recurrent disease 5 years after diagnosis. Although always at risk for relapse, 92% of cancer patients who are disease-free at 5 years are expected to be alive 15 years after diagnosis. Effort must be focused on health issues that result from the cancer or its treatment.

Late effects vary with the primary disease, its location and treatment, and genetic or other underlying medical problems. Many late effects develop slowly and are not

evident at the end of therapy. Accordingly, the follow-up of survivors should be tailored to monitor for specific risk factors and should change as time from diagnosis increases (Tables 1 and 2). Many of the more serious long-term effects require early recognition and management for the most favorable outcome. A guideline for long-term follow-up of patients who have acute lymphoblastic leukemia (ALL) is provided (Table 3). Although ALL is the most common malignancy of childhood, the incidence of late effects is relatively low. Late effects of surgery are determined by the specific procedure and are not discussed further.

Table 3. Monitoring for Late Effects in Patients Treated for Acute Lymphoblastic Leukemia*

System	Concern	Monitoring	Frequency
Hematologic	Relapse**	Complete blood count and physical examination	1st year: monthly 2nd year: every 2 to 3 months 3rd year: every 3 to 4 months 4th year: every 6 months 5th year and after: yearly
Cardiac	Congestive heart failure	Echocardiography	Age and cumulative anthracycline dose-dependent (see Table 4)
Neurocognitive	School performance	History Neuropsychological evaluation	Yearly As indicated
Orthopedic	Avascular necrosis	History and physical examination Radiographs or magnetic resonance imaging	Yearly As indicated
	Osteoporosis	Dual energy x-ray absorptiometry	Baseline by age 18 y, then as indicated

*Very few children now require cranial radiation as part of therapy. In those who have had cranial radiation, endocrine studies also should be performed as clinically indicated.
 **Persistent myelosuppression can occur for up to several months after completion of therapy. If counts remain abnormal beyond 6 months after cessation of therapy, a hematologist should be consulted and a bone marrow aspiration considered.

Neurocognitive Sequelae

Patients who receive cranial radiation or either methotrexate or cytarabine administered intrathecally or intravenously in high doses are at risk for neurocognitive dysfunction (Tables 1 and 2). Most have brain tumors or acute leukemia and require therapy of the central nervous system. Deficits of attention span, short-term memory, speed of mental processing, visual-motor coordination, or sequencing abilities are common. Intellectual decline is more apparent in children treated at a younger age and is proportional to the dose of radiation or intensity and duration of chemotherapy. More subtle cognitive damage may not be evident until academic work becomes more demanding. A formal neuropsychological evaluation should be performed by an experienced professional at the end of therapy if any neurocognitive dysfunction is suspected and then periodically as indicated. Individualized recommendations for school can be made, and the indications and benefits of attention-focusing medications discussed.

Hearing loss can result from chemotherapy (primarily cisplatin) or cranial radiation (Tables 1 and 2). Cisplatin can cause high-frequency sensorineural hearing loss (Table 2). Conductive hearing loss can occur in patients receiving cranial irradiation because of stimulation of cerumen production that causes impaction of the tympanic canal. Audiograms should be performed if hearing loss is suspected or learning difficulties are encountered.

Cardiotoxicity

Anthracycline use is the most common cause of heart damage in pediatric cancer survivors. The risk for cardiotoxicity increases with higher cumulative doses of anthracyclines and is related to female sex, younger age, trisomy 21, radiation involving the heart, and exposure to alkylating agents. Controversy remains over the maximum safe dose of anthracyclines because toxicity may occur with relatively low doses. In younger children, follow-up is essential regardless of dose. Agents to reduce the risk of cardiac toxicity without compromising effects on the tumor are under study. Screening with echocardiography and electrocardiography should be performed every 1 to 5 years, depending on the cumulative anthracycline dose and other risk factors (Table 4).

Cardiac radiation can cause chronic pericarditis and may increase the risk of early-onset coronary artery disease (Table 1). Familial risks, presence of hyperlipidemia, and results of stress testing, when indicated, should be addressed.

Endocrinopathies

Endocrine abnormalities are common late effects and usually can be treated. The pituitary, thyroid, and gonads are affected most. Cranial radiation predisposes patients to growth hormone deficiency. Like most endocrine effects, the degree of damage correlates with the radiation dose. Doses greater than 3,000 cGy usually cause

Table 4. Frequency of Echocardiograms for Patients Treated With Anthracyclines

Age at Treatment	Total Anthracycline Dose*	Recommended Frequency of Monitoring
Any	>300 mg/M ²	Every year
<1 year old	Any	Every 1 to 2 years [†]
>1 year old	<300 mg/M ²	Every 2 to 5 years [†]

*Based on equivalent mg of doxorubicin/daunorubicin.
[†]More frequently if patient had radiation to the chest.

growth hormone deficiency, but it can occur with doses as low as 1,800 cGy. Chemotherapy in combination with cranial radiation contributes to growth hormone deficiency. Patients should be monitored for height, weight, body mass index percentiles, and SMR staging, with comparisons made to family patterns.

Hypothyroidism can result from radiation of the pituitary (>3,000 cGy) or the thyroid gland (>2,000 cGy). Hypothyroidism occurs in up to 50% of patients who received radiation to the thyroid gland and can take years to develop. Female sex, higher radiation doses, and older age are risk factors for hypothyroidism. Free thyroxine and thyroid-stimulating hormone should be monitored yearly. Hyperthyroidism, thyroid nodules, and thyroid cancer also are more likely to develop following thyroid radiation (Table 1).

Alkylating agents and gonadal radiation can impair fertility and sexual development (Tables 1 and 2). Efforts are being made to restrict or omit alkylating agents because they increase the risk of sterility. Unfortunately, they are very effective agents, especially in treating solid tumors. Males treated with alkylators or testicular radiation retain endocrine function at higher doses than females, but spermatogenesis is more sensitive. Younger boys demonstrate less of an effect on sperm production, but prepubertal boys are not spared. Sperm banking should be encouraged in adolescent boys to circumvent the sterilizing effects of therapy.

In females, hormonal function correlates with the potential for fertility. Because of the decreasing number of oocytes, the risk of menstrual irregularities, premature ovarian failure, and infertility increases with older age at treatment. Prepubertal females tolerate high doses of alkylating agents, but high doses of radiation may cause premature ovarian failure, leading to failure to develop secondary sexual characteristics. Adolescent girls often

recover gonadal function after therapy, but are at risk for premature menopause, with a decrease in years of potential fertility. Survivors should be monitored with regard to puberty, menses, sexual function, and SMR staging. Luteinizing hormone, follicle-stimulating hormone, and testosterone or estradiol should be measured, with referral to an endocrinologist if indicated.

Secondary Malignancies

The cumulative risk at 20 years for second malignant neoplasms in survivors of pediatric cancer is 3% to 10%, which is 5 to 20 times greater than for the general population. Much of this risk is associated with therapies known to be carcinogenic. Radiation is associated with the development of cancer in the radiation field, notably, breast cancer, thyroid cancer, skin cancers, brain tumors, and most commonly, bone and soft-tissue sarcomas (Table 2). Epipodophyllotoxins (ie, etoposide) and alkylating agents are associated with secondary development of acute myeloid leukemia (Table 2). Patients treated with cyclophosphamide have a higher risk of developing bladder cancer (Table 2). For some, a genetic defect results in an increased risk for specific cancers.

Certain diseases require special mention. Secondary malignancies are particularly common in survivors of Hodgkin disease and include acute myeloid leukemia, nonHodgkin lymphoma, breast cancer, and other solid tumors. The risk for some of these malignancies increases with time. Children who have the genetic form of retinoblastoma, which includes all who have bilateral disease and about 10% of children who have unilateral disease, have a 50% chance of developing a secondary malignancy, regardless of whether they are treated. Hepatoblastoma has been associated with familial polyposis coli, and survivors should be screened for colon cancer.

Survivors should be informed of their risks for developing secondary cancers and should be evaluated yearly by a clinician familiar with their treatment and risks.

Psychosocial Effects

Efforts recently have focused on the psychosocial impact of cancer and its treatment on survivors. In 1994, “learning that one/one’s child has a life-threatening disease” was included in the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition as an event sufficiently traumatic to precipitate posttraumatic stress disorder (PTSD). The traumatic impact of being given the diagnosis and of experiencing treatment that can include painful, invasive procedures, frequent hospitalizations, separations from family and friends, and fear of the unknown is great. It is estimated

that PTSD occurs in about 5% to 20% of survivors of childhood cancer and in 6% to 25% of their mothers. Recent data suggest that cancer-related PTSD emerges in young adulthood and may affect the achievement of developmental milestones. Young adulthood is a time of increased vulnerability and major psychosocial challenges that may require, perhaps for the first time, a focus on the effects of cancer and its treatment. The impact seems to be associated more with survivors' perceptions of treatment and its effects rather than with more objective medical data. Counseling can help survivors and their families work through these issues in a healthy manner.

A recent study showed that a large proportion of survivors were functioning well and leading normal lives, but there was a subgroup that was less likely to complete high school and more likely to have learning disabilities. The percentage of employed survivors was lower than the percentage of employed controls. Survivors had lower rates of marriage and parenthood. Poor adjustment, depression, and diminished functioning in the area of social contacts and friendships may account for some of these findings.

Denial of insurance coverage and other examples of discrimination are concerns for the survivor. It may be difficult to obtain life and health insurance. Entrance into the military has been denied. Job discrimination is much less common now that laws are in place to protect survivors. Cancer survivors have addressed such issues by working with national organizations such as the Candlelighters or the National Coalition for Cancer Survivorship.

Summary

Health-promoting behaviors for cancer survivors should be stressed and evaluations limited to those that are cost-effective and have a defined intervention. All survivors of childhood cancer should receive regular medical

care throughout life from a physician who is aware of their treatment and is comfortable with risk-based monitoring for specific late effects. Most pediatric oncology programs can provide or assist in this care. Survivors now are reaching an age when adult follow-up is more appropriate. Therefore, pediatricians, internists, and family practitioners all are encouraged to take a more active role in caring for cancer survivors and educating themselves about the risks for late effects.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

10. Which of the following *most* correctly describes the risk of cardiotoxicity from anthracycline chemotherapy?
 - A. Cardiac function should be monitored every 1 to 5 years depending on the total cumulative dose.
 - B. Cumulative doses of $<300 \text{ mg/M}^2$ are safe.
 - C. Klinefelter syndrome increases this risk of cardiotoxicity.
 - D. Males are at greater risk for cardiotoxicity.
 - E. Younger age at diagnosis decreases the risk for cardiotoxicity.
11. A 17-year-old female, who is new to your practice, was treated for Hodgkin disease with chemotherapy and involved field radiation at age 9 years. Her Internet research has made her concerned about her risk for thyroid disease. In counseling her, which of the following is *correct*?
 - A. Her risk is reduced because she is a female.
 - B. Her risk of developing hypothyroidism is 5% to 10%.
 - C. Her risk of developing thyroid cancer is minimal.
 - D. She already would have developed hypothyroidism if it were to occur.
 - E. Thyroid function should be evaluated annually.
12. The risk of developing secondary malignancies is particularly high in children who were treated for which of the following malignancies?
 - A. Acute lymphoblastic leukemia.
 - B. Chronic myelogenous leukemia.
 - C. Hodgkin disease.
 - D. NonHodgkin lymphoma.
 - E. Wilms tumor.